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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,812	HUANG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,9-12,17 and 42-54* is/are pending in the application.

4a) Of the above claim(s) *10 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,9,11,12,17,42-50 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1, 2, 4-5, 9, 11, 12, 17, 42-50, 52-54, species SEQ ID NO:42, wherein claims 1, 2, 4-5, 11, 12, 17, 42-50, 52-54 are generic to the species SEQ ID NO:42, in the reply filed on 01/20/06 is acknowledged.

In the reply of 01/20/06 Applicant traverses the holding of non-responsiveness for not identifying the claims readable on the elected species, because no such requirement was made in the previous Office action of 09/27/05.

After review and reconsideration, the Office action of 12/28/05 is withdrawn.

Accordingly, group I, claims 1, 2, 4-5, 9, 11, 12, 17, 42-50, 52-54, species nonapeptide SEQ ID NO:42 are examined in the instant application.

It is noted that the embodiments of claims 4, 44, 47, as drawn to a nonapeptide, wherein the amino acid adjacent to the N-terminal amino acid is M, and the C-terminal acid is V or I has been withdrawn from consideration, as being drawn to non-elected species.

Similarly, the embodiment of new claim 51, as drawn to a decapeptide, is withdrawn from consideration, as being drawn to a non-elected species.

Since applicant has elected Group I, species the nonapeptide SEQ ID NO:42, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claim 51, drawn to a decapeptide, have been

withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03.

Newly submitted claim 51 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The decapeptide of claim 51 is structurally and functionally distinct from a nonapeptide, and thus is a distinct invention, in view that unity does not exists in the instant application, because the technical feature of group I, SEQ ID NO:1 is known in the art (De Plaen, 1994, of record).

Moreover, a decapeptide is not generic to a nonapeptide, which has different properties and characteristics as compared to a nonapeptide, such as amino acid positions responsible for anchoring or binding and response to CTLs (see WO 94/020127, page 57, table 15, which describes the different properties of 9-mers and 10-mers).

OBJECTION

1. Claims 1, 2, 17, 44-50, 52-54 are objected to, because claims 1, 2, 17 contains periods (.) that are not at the end of the claim. The objection can be obviated by amending the claims, for example, to delete the periods and substitute therewith a colon.

2. Claim 12 is objected to, because claim 12 does not further limit claim 11, which depends on claim 4. The property of "comprising an unbroken sequence of amino acids from SEQ ID NO:1" in claim 12 is the property of the nonapeptide of claim 4.

Further, if claim 12 is interpreted as comprising any unbroken sequence of amino acids from SEQ ID NO:1, claim 12 actually broadens the scope of claim 12.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1, 2, 11-12, 17, 44-50, 52-54 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1, 2, 4-5,11-12, 17, 44-50, 52-54 are drawn to:

1) An isolated polypeptide "comprising" an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1 (claim 1), or that elicits an immune response from human lymphocytes (claim 2).

2) An isolated polypeptide of up to about 93 amino acids in length, characterized by "comprising" a nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, other than the nonapeptide SEQ ID NO:57 (claims 11, 12).

3) The isolated polypeptide of claim 1, wherein the amino acid sequence of said isolated polypeptide is not that set out in either SEQ ID NO:1, 2 or that coded for by nucleotides 334-918 of SEQ ID NO:7 (claim 17).

4) The isolated polypeptide of claim 1, or claim 2, wherein the polypeptide being a nonapeptide, wherein wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 44-49).

5) The polypeptide of claim 1, other than the nonapeptide SEQ ID NO:48, 49 or 50 (claim 50).

6) The polypeptide of claim 1, wherein the polypeptide elicits an immune response from human lymphocytes, when complexed with with histocompatibility complex molecule type HLA-A2 (claim 52-53).

7) An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, wherein the polypeptide elicits an immune response from human lymphocytes, and "wherein the immune response is a cytolytic response from human T-lymphocytes" (claim 54).

The specification discloses that the nonapeptide SEQ ID NO:42, and the decapeptide SEQ ID NO:44 from MAGE-10 SEQ ID NO:1 could sensitise a melanoma cell line expressing MAGE-10 to lysis by CTLs (p.32).

It is noted that SEQ ID NO:1 is MAGE-10 of 369 amino acids in length, which is relatively large and would contain numerous peptide epitopes for T cells, the structure of which are not disclosed in the specification, except for SEQ ID NO:42 and 44.

It is further noted that the language "the polypeptide being a nonapeptide" in claims 44, 47, is interpreted as an open language, and has the same meaning as "comprising".

A. Due to the open language "comprising" of claims 1-2, 11-12, 17, 44-50, 52-54 encompasses unknown sequences that are attached to a fragment of SEQ ID NO:1, wherein said fragment could be a nonapeptide, and wherein said fragment could complex with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, or elicit an immune response from human lymphocytes, and wherein the immune response could be a cytolytic response from human T-lymphocytes.

It is note that complexing with HLA-A2 is not a critical function of the claimed polypeptide, because binding with HLA molecule does not necessarily leads to eliciting a response from CTLs, because T cell receptors have to recognize a specific combination of antigen and MHC. This is clearly shown by the teaching of Kirkin et al, APMIS, 1998, 106: 665-679, that only few peptides from melanoma associated antigens have been so far identified as being recognized by specific CTLs, and that some Melan-A/MART-1 peptides although having high affinity for HLA-A2.1 antigen do not induce the generation of melanoma specific CTLs in vitro.

Further, there is no correlation between structure of the claimed sequences and the function of eliciting an immune response or eliciting cytolytic response by T cells specific for SEQ ID NO:1, because the effect of the attached sequences with unknown structure on the conformation of the claimed polypeptide is unpredictable, and one cannot predict whether the claimed polypeptides would have similar conformation as SEQ ID NO:1 and expose on its surface said unbroken sequence or nonapeptide of SEQ ID NO:1, such that B cells or T cells specific for said unbroken sequence or

nonapeptide of SEQ ID NO:1 would recognize cells expressing the claimed polypeptides. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Bowie et al also teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306).

In view of the above, **there is no correlation between structure of the claimed sequences and the function of eliciting an immune response or eliciting cytolytic response by T cells specific for SEQ ID NO:1.**

Further, the recited SEQ ID NO:1 is not a representative species for the claimed polypeptides comprising an unbroken sequence of SEQ ID NO:1.

B. Further, Claims 2, 47-49, 52- 54 encompasses a genus of peptides, or nonapeptides derived from the MAGE-10 protein SEQ ID NO:1, that are linear or conformational epitopes of B cells or T cells, wherein said peptides could induce in vivo immune response from human lymphocytes, or lysis of cells such as melanoma cells expressing SEQ ID NO:1 by T cells.

It is noted that peptides from several proteins of the MAGE family usually have low immunogenicity, and that not any peptide could induce in vivo immune response in human. Kirkin et al, 1998, teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, especially p.666, second column, second paragraph, last 6 lines).

Similarly, Visseren et al, 1997, Intl J Cancer, 73(1): 125-30. teach that not all peptides from MAGE-2 are immunogenic and produce an immune response in vivo in mice (p.127, first column, third paragraph).

Further, it is well known in the art that antigen peptides have to fit into and binds to B cell antigen receptors, which are immunoglobulins on B cell surface for activation of B cells (Stites et al, 1997, Medical Immunology, 9th ed, Appleton & Lange, Stamford, Connecticut, figure 3-9 on page 51, pages 50-51, 118-119). It is also well known in the art that T cell receptors recognize the ligands comprising peptide antigens that are bound to MHC molecules, and that individual T cells respond only to a specific combination of antigen and MHC (Stites et al, 1997, Medical Immunology, 9th ed, Appleton & Lange, Stamford, Connecticut , page 130). In other words, not any peptides of a sequence could elicit T cell response, because T cell receptors have to recognize a specific combination of antigen and MHC. This is clearly shown by the teaching of Kirkin

et al, supra, that only few peptides from melanoma associated antigens have been so far identified as being recognized by specific CTLs, and that some Melan-A/MART-1 peptides although having high affinity for HLA-A2.1 antigen do not induce the generation of melanoma specific CTLs in vitro.

It is further noted that peptide epitopes of T cells could be linear or conformational to fit into the three dimensional structure of the T cell receptor, and that each peptide epitope of individual set of B cells or T cells is structurally and/or conformationally different from each other, because of difference in the structure of individual set of T cell receptors. However, there is no teaching in the specification of whether or not the claimed epitopes are linear or comprise 3-dimensional structures, nor the 3-dimensional structure of the claimed peptide epitopes is disclosed. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by T cell receptors the claimed invention. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

The specification has not identified which amino acid fragments are critical or essential characteristics of the claimed linear and conformational B and T cell epitopes, other than the linear peptides of SEQ ID NO:42 and 44, that elicit CTL response.

The recited SEQ ID NO:42 and 44 are not representative species of the claimed genus of peptide epitopes from SEQ ID NO:1, that could elicit an immune response or cytolytic response from human T-lymphocytes.

Moreover, there is no known common structure of the claimed genus of T or B cell peptide epitopes from SEQ ID NO:1, nor is there disclosure of any correlation between common structure of the claimed epitopes and critical function, i.e. eliciting immune response from human lymphocytes, or lysis of cells such as melanoma cells expressing SEQ ID NO:1 by T cells.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that □[a] written description of an invention involving a chemical genus, like a description of a chemical species, □requires a precise definition, such as by structure, formula, [or] chemical name,□ of the claimed subject matter sufficient to distinguish it from other materials.□ Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as □vertebrate insulin cDNA□ or □mammalian insulin cDNA□ without more, is not an adequate written description of the

> genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that □naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.□ Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. □A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.□ Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by □show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying

characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. □ Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

In this case, the specification does not describe a polypeptide comprising an unbroken sequence of SEQ ID NO:1, or a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response or elicits a cytolytic response from human T-lymphocytes in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide the complete structure of a polypeptide comprising an unbroken sequence of SEQ ID NO:1, or a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response or elicits a cytolytic response from human T-lymphocytes, other than SEQ ID NO:1 and its peptides, SEQ ID NO:42 and 44, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO:1, and its peptides SEQ ID Nos 42 and 44, that elicit T cell response, this does not provide a description of a polypeptide comprising an unbroken sequence of SEQ ID NO:1, or a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response or elicits a cytolytic response from human T-lymphocytes, that would satisfy the standard set out in the example in Enzo.

The specification also fails to describe a polypeptide comprising an unbroken sequence of SEQ ID NO:1, or a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response or elicits a cytolytic response from human T-lymphocytes, by the test set out in the example in Lilly. The specification describes only SEQ ID NO:1, and its linear peptides of SEQ ID Nos 42 and 44, that induce T cell response. Therefore, it necessarily fails to describe a "representative number" of such species, which includes unknown sequences, having unknown conformational T cell epitopes, in addition to linear T cell epitopes of unknown and diverse structure, because each epitope has a unique structure, whether it is linear or conformational. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a polypeptide comprising an unbroken sequence of SEQ ID NO:1, or a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response or elicits a cytolytic response from human T-lymphocytes, that is required to practice the claimed invention.

For the reasons set forth above, the specification does not meet 112, first paragraph, written description requirement.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1, 2, 4-5, 9, 11, 12,17, 42-50, 52-54 are rejected under 35 U.S.C. 112, first paragraph.

Claims 1, 2, 4-5, 9, 11, 12,17, 42-50, 52-54 are drawn to:

1) An isolated polypeptide "comprising" an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1 (claim 1), or that elicits an immune response from human lymphocytes (claim 2).

2) A nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, other than the nonapeptide SEQ ID NO:57 (claim 4).

3) A nonapeptide of claim 4, wherein the amino acid in position 3 is Y and/or the amino acid in position 4 is D and/or the amino acid in position 5 is G and/or the amino acid in position 7 is E and/or the amino acid in position 8 is H (claim 5).

4) A nonapeptide having the amino acid sequence SEQ ID NO:42 (claim 9).

5) An isolated polypeptide of up to about 93 amino acids in length, characterized by "comprising" a nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, other than the nonapeptide SEQ ID NO:57 (claims 11, 12).

6) The isolated polypeptide of claim 1, wherein the amino acid sequence of said isolated polypeptide is not that set out in either SEQ ID NO:1, 2 or that coded for by nucleotides 334-918 of SEQ ID NO:7 (claim 17).

7) The isolated nonapeptide of claim 4, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 42-43).

8) The isolated polypeptide of claim 1, or claim 2, wherein the polypeptide being a nonapeptide, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 44-49).

9) The polypeptide of claim 1, other than the nonapeptide SEQ ID NO:48, 49 or 50 (claim 50).

10) The polypeptide of claim 1, wherein the polypeptide elicits an immune response from human lymphocytes, when complexed with histocompatibility complex molecule type HLA-A2 (claim 52-53).

11) An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, wherein the polypeptide elicits an immune response from human lymphocytes, and "wherein the immune response is a cytolytic response from human T-lymphocytes" (claim 54).

The specification discloses that the nonapeptide SEQ ID NO:42, and the decapeptide SEQ ID NO:44 from MAGE-10 SEQ ID NO:1 could sensitise a melanoma cell line expressing MAGE-10 to lysis by CTLs (p.32).

The specification discloses that MAGE 10 is detected in several tumors by PCR (Example 6 on pages 34-35).

The specification contemplates diagnosing diseases, preferably cancer, using an agent specific for the polypeptide of the claimed invention (p.7). The specification further contemplates producing CTLs reactive to tumor cells (p.7) and treating disorders characterized by expression of the polypeptide, using CTLs (p.15-16).

One cannot extrapolate the teaching in the specification to the enablement of the claims. One cannot predict that a polypeptide comprising a fragment or a nonapeptide of SEQ ID NO:1, or the nonapeptide SEQ ID NO:42 could be used for producing antibodies or CTLs effective for diagnosis or treatment of diseases associated with SEQ ID NO:1, and especially cancer, because one cannot predict that the polypeptide SEQ ID NO:1 is expressed in an adequate amount on primary cancer cell surface, or cells from tissues with diseases .

It is noted that although the specification discloses that MAGE 10 is detected in several tumors by PCR, the level of expression was not disclosed. De Plaen E et al, 1994, Immunogenetics, 40: 360-369, however, teach that as detected by PCR, the level of expression of several MAGEs, including MAGE-10 are very weak in all of various tumors examined, and that the amount of RNA of these genes represent less than 1% of that of the highly expressed gene (p.367, first column, second paragraph).

One cannot predict whether any protein product is actually produced, or even if translated, whether the protein is expressed in adequate amount to be useful as a target for antibodies or CTLs, in view that protein levels cannot predictably be correlated with steady-state mRNA levels or alterations in mRNA levels.

Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-ranslational level. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

In view of the above teaching in the art, and in view that the expression of the encoding polynucleotide is very weak in all tumors examined, as taught by De Plaen E et al, one cannot predict that adequate amount of the MAGE-10 polypeptide SEQ ID NO:1 is expressed on primary cancer cells, or diseased tissues such that antibodies or CTLs specific for the nonapeptide of SEQ ID NO:42 could recognize, or lyse, respectively, primary cancer cells or diseased tissues. This possible problem with insufficient quantity of SEQ ID NO:1 expressed on malignant cells could further be exacerbated, in view that cancer cells could downregulate the expression of tumor antigens, and thus reducing the amount of the antigens presented, and consequently the possibility of being recognized and lysed by CTLs, and further in view of the well-known cancer tolerance phenomena. For example, White et al, 2001, Ann Rev Med, 52: 125-145, teach that antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484).

Further, although a melanoma cell line expressing MAGE-10 is lysed by CTLs specific for SEQ ID NO:1, one cannot determine that primary cancer cells would express similar amount of MAGE-10 on their cell surface, such that primary cancer cells would be recognized the antibodies or lysed by CTLs specific for SEQ ID NO:1, because expression of antigens on primary cancer cells cannot predictably to be the same as that of cancer cells in culture, due to cell culture artifacts. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian, J et al, 2004, Physiol Genomics, 17: 170-182, teach culture-induced artifact in

macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke D L et al, 2003, Cancer Genetics and Cytogenetics 241: 137-141, teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments). Zaslav A L et al, 2002, Amer J Medical Genetics 107: 174-176, teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p. 175, first column, paragraph under Discussion).). Kunkel, P, et al, 2001, Neuro-oncology 3(2): 82-88, teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract).

The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

Further, cancer treatment using a MAGE peptide is unpredictable. This unpredictability applies as well to diseases associated with SEQ ID NO:1. Although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, especially p.666, second column, second paragraph, last 6 lines). In view of the extreme limited number of peptide (i.e. only one identified so far) from MAGE proteins that could induce CTLs having in vivo anti-tumor activity, one cannot determine that SEQ ID NO:42, or SEQ ID NO:1 contains peptides that could elicit specific CTLs with high affinity, that recognize and kill in vivo malignant cells.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order

to be enabling."

Given the above unpredictability, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 4-5, 11-12, 42-43 are still rejected under 112, first paragraph, because one cannot predict that the claimed nonapeptide could bind to HLA-A2 molecule and elicits a CTL response useful for diagnosis or treatment of diseases, especially cancer.

It is noted that the nonapeptide of claim 4 encompasses the sequence XLXXXXXXL, wherein the amino acid at position 1, 3-8 could be any amino acid.

The nonapeptide of claim 5 encompasses the sequence XLY(X or D) (X or G) (X or E) (X or H) L, wherein the amino acids at position 1 could be any amino acid, and amino acids at positions 4-8 could be any amino acid or could be amino acids D, G, E or H, respectively.

One cannot predict that the claimed nonapeptide of claim 4 could bind to HLA-A2 molecule and elicit CTL response useful for diagnosis or treatment of diseases associated with SEQ ID NO:1,such as cancer, in view of the following teaching of WO 94/020127 A1, Visseren, M JW et al, 1997, Intl J Cancer, 73(1): 125-30, and further in view of the unpredictability of cancer treatment, using a MAGE peptide, as taught by Kirkin et al, supra.

WO 94/020127 A1 teaches that for A2.1 motif for 9-mer peptides, the acidic amino acids and P at position 1, the acidic and basic amino acids at position 3, the basic amino acids at position 6, and the acid and basic amino acids at position 7 would have negative effect for the peptide binding to HLA-A2.1 (p.49 and table 9 on page 50).

Thus since the amino acid at position 1, 3, 6, and 7 of the claimed nonapeptide could be any amino acids, and since the effects of such amino acids on the binding of the nonapeptide sequence cannot be predicted, one cannot predict that the claimed nonapeptide sequences could bind to HLA-A2 molecule with sufficient affinity and elicit an immune or CTL response for use in diagnosis or treatment of cancer.

Further, Visseren et al teach that even some peptides of MAGE-2, that fit into the binding motif for binding to HLA-A0201, do not bind to the HLA molecule with sufficient affinity (p.127, first column, first paragraph). Indeed, one of the peptide, M2 15-23, which seems to be the same as the claimed nonapeptide of claim 4, does not bind to HLA-A2 with sufficient affinity (Visseren et al, table I on page 127). Further, Visseren et al teach even some peptides that bind to the HLA molecule with high affinity at 4^0 C, they do not bind with high affinity at 37^0 C, and therefore are less likely to form stable complexes in vivo and have a lower chance to appear in HLA-A0201 molecule at the cell surface (p.127, first column, second paragraph). Visseren et al teach that not all peptides from MAGE-2 are immunogenic and produce an immune response in vivo in mice (p.127, first column, third paragraph).

In addition, although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-

A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (Kirkin et al, supra).

Thus in view of the above teaching of in the art, one cannot predict that the claimed nonapeptides would bind to HLA-A2 molecule with sufficient affinity to induce an immune response or a CTL response useful for diagnosis or treatment of diseases associated with SEQ ID NO:1, such as cancer.

Further, one cannot predict that the claimed nonapeptide could be used for diagnosis of diseases associated with SEQ ID NO:1, such as cancer, in view that the structure of the claimed nonapeptide is drastically different from SEQ ID NO:42, one cannot predict that antibody to the claimed nonapeptide would not cross react with a sequence different from SEQ ID NO:1, and thus would be non-specific.

Given the above unpredictability, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

3. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 1-2, 11-12, 17, 44-50, 52-54 are still rejected under 112, first paragraph, because one cannot predict that the unbroken sequence of SEQ ID NO:1 or the nonapeptide would be exposed on the surface of the claimed sequence comprising said unbroken sequence or nonapeptide, in view of the teaching of Bowie et al (Science, 1990, 257:1306-1310), supra.

As such, one cannot predict that B cells or T cells specific for SEQ ID NO:1 would recognize cells expressing the claimed polypeptides.

Given the above unpredictability, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 1-2, 17, 44-50, 52-54 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,912,143.

Claims 1-2, 17, 44-50, 52-54 are drawn to:

1) An isolated polypeptide "comprising" an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1 (claim 1), or that elicits an immune response from human lymphocytes (claim 2).

2) The isolated polypeptide of claim 1, wherein the amino acid sequence of said isolated polypeptide is not that set out in either SEQ ID NO:1, 2 or that coded for by nucleotides 334-918 of SEQ ID NO:7 (claim 17).

3) The isolated polypeptide of claim 1, or claim 2, wherein the polypeptide "being" a nonapeptide, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 44-49).

4) The polypeptide of claim 1, other than the nonapeptide SEQ ID NO:48, 49 or 50 (claim 50).

5) The polypeptide of claim 1, wherein the polypeptide elicits an immune response from human lymphocytes, when complexed with histocompatibility complex molecule type HLA-A2 (claim 52-53).

6) An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, wherein the polypeptide elicits an immune response

from human lymphocytes, and wherein the immune response is a cytolytic response from human T-lymphocytes (claim 54).

It is noted that the language the polypeptide "being" a nonapeptide is interpreted as an open language, and has the same meaning as "comprising".

US 5,912,143 teaches SEQ ID NO:4, which is 100% similar to the full length SEQ ID NO:1, from amino acid 1 to amino acid 369 under MPSRCH sequence similarity search (MPSRCH search report, 2006, us-09-856-812b-1.olig.rai, pages 1-2).

SEQ ID NO:4 from US 5,912,143 comprises a nonapeptide sequence which is the same as the claimed SEQ ID NO:42, in which the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal acid is L (MPSRCH search report, 2006, us-09-856-812b-1_copy_254-262.olig.rai, pages 1-2).

The polypeptide taught by the art seems to be the same as the claimed polypeptide, and clearly is not SEQ ID NO:2 or coded for by nucleotides 334-918 of SEQ ID NO:7.

Although the reference does not specifically teach that the polypeptide complexes with a major histocompatibility complex molecule type HLA-A-2, preferably HLA-A2.1, or that elicits an immune response from human lymphocytes, wherein the immune response is a cytolytic response form human T lymphocytes, however, the claimed polypeptide appears to be the same as the prior art polypeptide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of

evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claims 1, 4, 11-12, 17, 42-46 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,682,731.

Claims 1, 4, 11-12, 17, 42-46 are drawn to:

1) An isolated polypeptide "comprising" an unbroken sequence of amino acids from SEQ ID NO:1, that complexes with histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1 (claim 1).

2) A nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, other than the nonapeptide SEQ ID NO:57 (claim 4).

3) An isolated polypeptide of up to about 93 amino acids in length, characterized by comprising a nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, other than the nonapeptide SEQ ID NO:57 (claims 11, 12).

4) The isolated polypeptide of claim 1, wherein the amino acid sequence of said isolated polypeptide is not that set out in either SEQ ID NO:1, 2 or that coded for by nucleotides 334-918 of SEQ ID NO:7 (claim 17).

5) The isolated polypeptide of claim 4 , wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 42-43).

6) The isolated polypeptide of claim 1 , wherein the polypeptide being a nonapeptide, wherein the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L (claims 44-46).

It is noted that a polypeptide of up to about 93 amino acids in length could be of any length, provided it is not more than 93 amino acids in length.

US 6,682731 teaches a nonapeptide sequence, SEQ ID NO:20 (column 13), which is the same as a nonapeptide fragment of the claimed SEQ ID NO:1, in which the amino acid adjacent to the N-terminal amino acid is L, and the C-terminal amino acid is L, as shown by sequence similarity search (MPSRCH search report, 2006, us-09-856-812b-1.olig_sz9.rai, page 3). US 6,682731 teaches that the peptide complexes with HLA-A2 molecule (column 13, lines 20-24).

US 6,682731 does not teach that SEQ ID NO:20 is a fragment of SEQ ID NO:2, or coded by nucleotides 334-918 of SEQ ID NO:7.

The polypeptide taught by US 6,682731 seems to be the same as the claimed polypeptide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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MINH TAM DAVIS

March 23, 2006

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